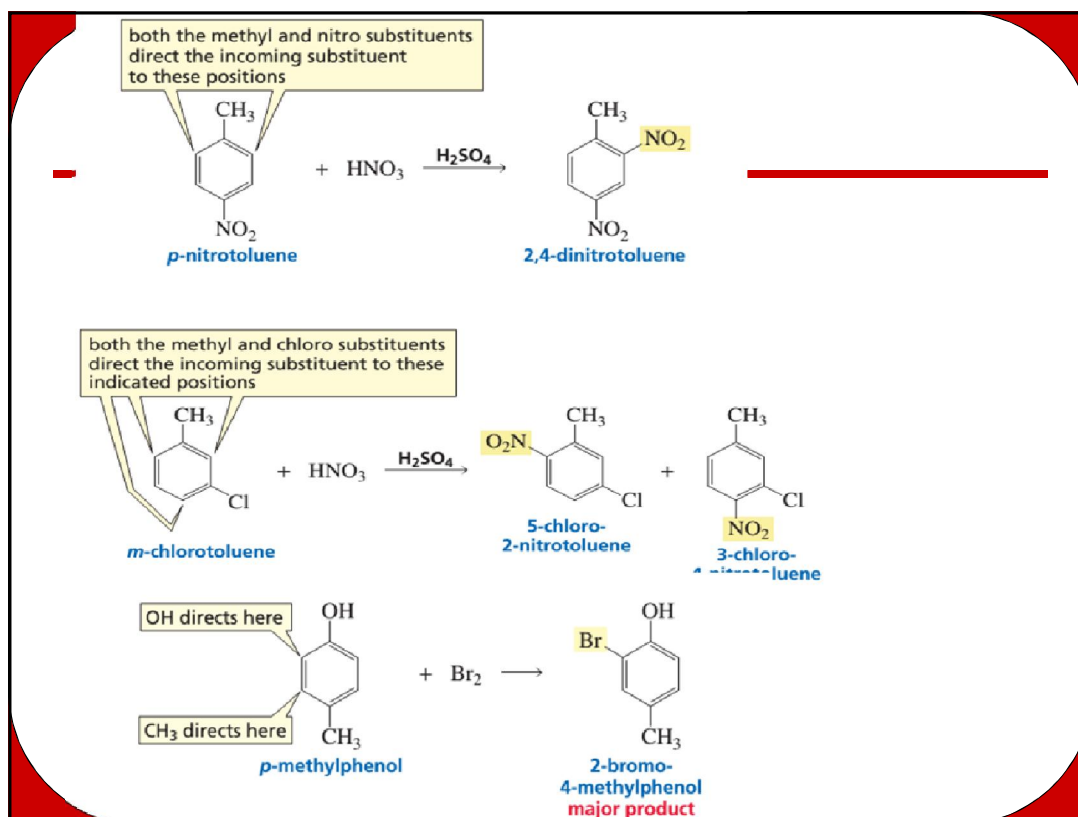




Medicinal Organic Chemistry

كيمياء عضوية دوائية

Dr.Mokhtar Al-Ghorafi





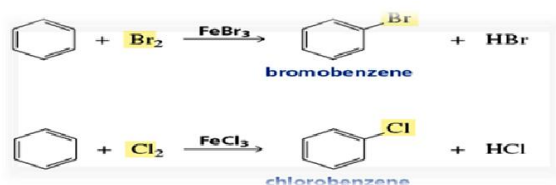
Aromatic halogen compounds

Aromatic halides

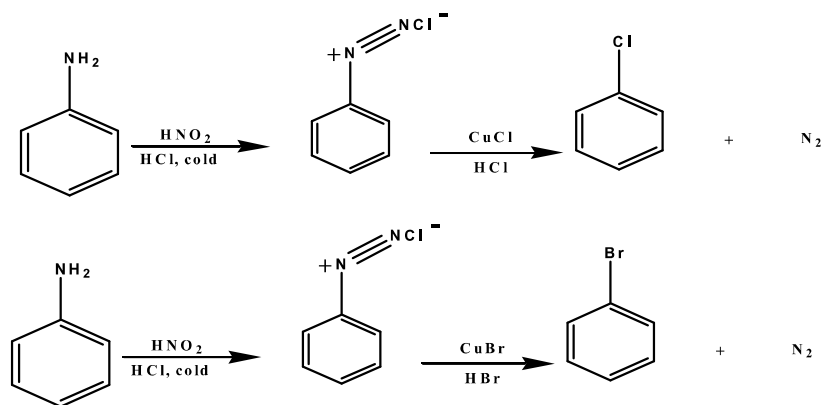
Aryl halides are compounds in which a halogen substituent is attached directly to an aromatic ring (Ar-X) e.g bromobenzene .

Methods of preparation

1) Direct halogenation

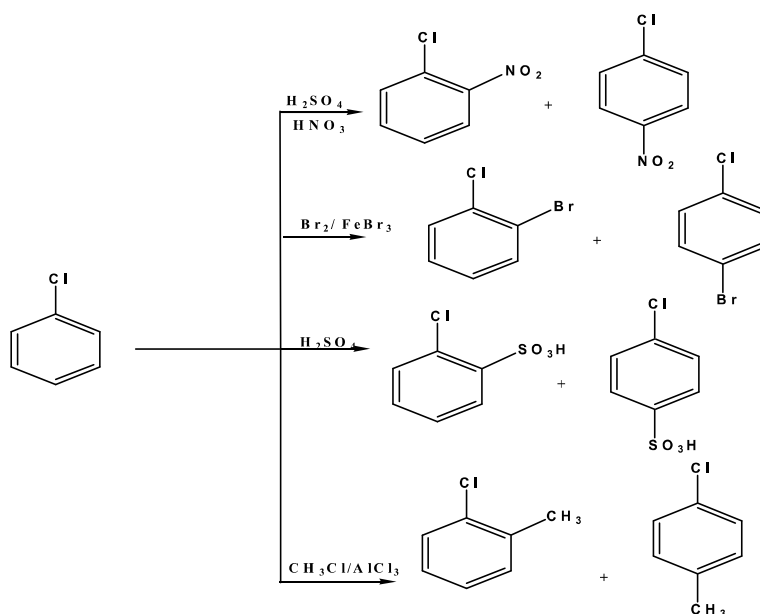


2) Indirect halogenation(from amine)Diazonium chloride



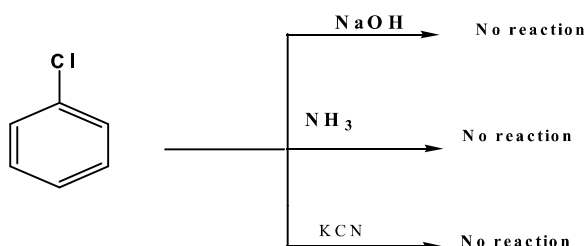
Reactions

Electrophilic aromatic substitution reactions(SE)



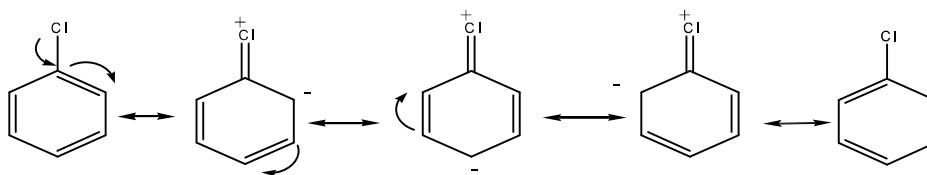
Nucleophilic Reactions:

Unlike alkyl halide, aryl halides do not undergo Nucleophilic reaction readily. The halogen bond can not be replaced by OH^- , NH_2^- , CN^- with aqueous sodium hydroxide, ammonia or potassium cyanide.



The reason for this unusual lack of reactivity is that C-X in aryl halides is short and strong compared to that in alkyl halides. this is so because

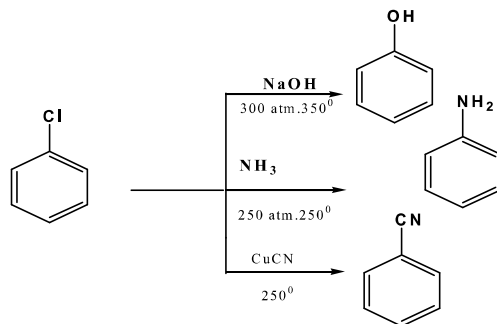
1. The carbon- chlorine bond in chloro benzene has some double bond character as a result of resonance.



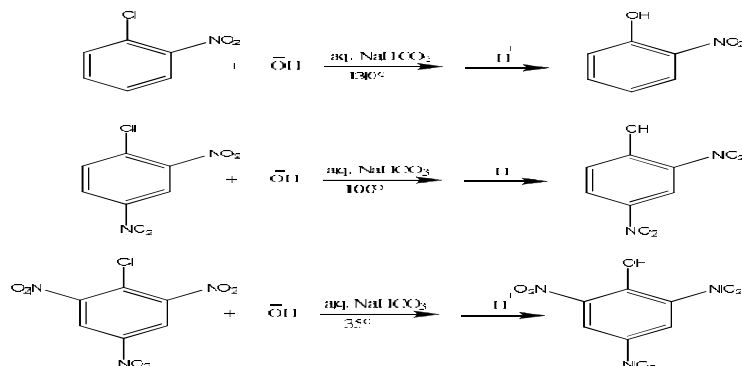
2. The aromatic ring with its localized π -electron cloud is considered a center of high electron density.

Nucleophilic displacement reactions in aryl halide require drastic or strong conditions to occur.

a) Under drastic conditions: the halogen of an aryl halide can be replaced by an OH, NH₂ and CN group when treated with appropriate nucleophilic reagents at high temperature and pressure. (Unimolecular substitution)

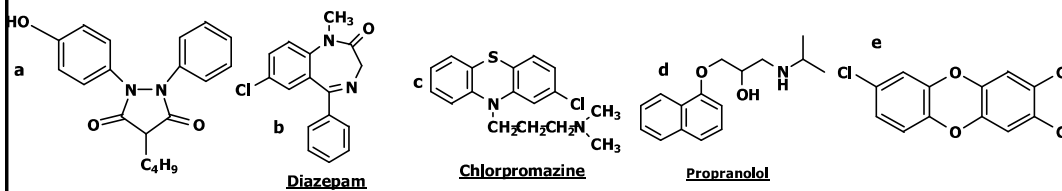


Explanation:

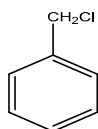


Q.3. One ring of the following drugs undergoes oxidation by liver enzymes (metabolism) much more readily than the other?

a) Which one is it? b) Explain your answer?



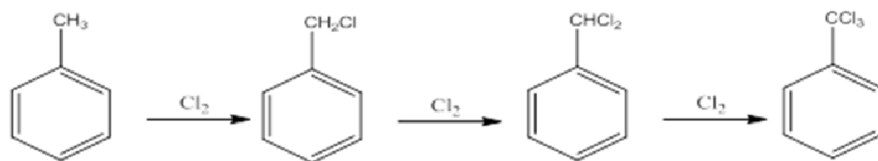
b- Aryl alkyl halides



benzyl chloride

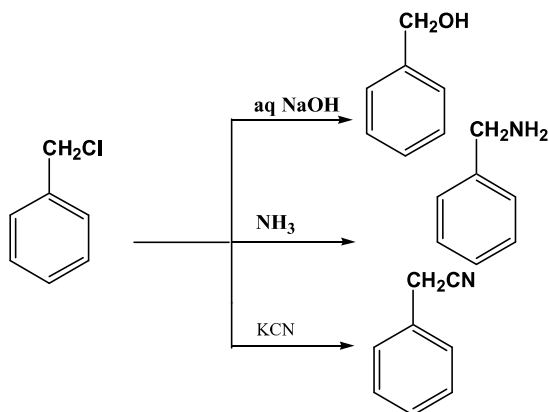
Preparation:

1- Chlorination of boiling toluene, in the absence of catalysts, in sunlight which can produce chlorine atoms and so initiate a chain reaction, gives benzyl chloride, benzylidene chloride (benzal chloride), and benzotrichloride.

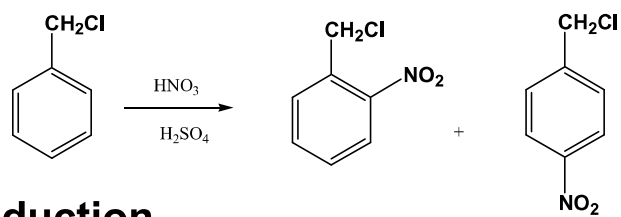


Reactions

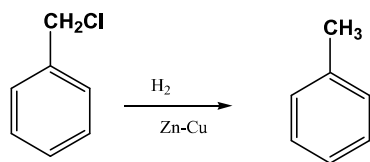
1. Nucleophilic substitution reactions:



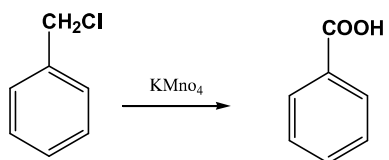
2. Electrophilic aromatic substitution reactions (SE)



3. Reduction

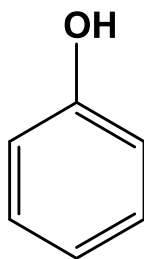


4. Oxidation



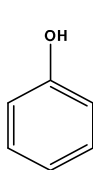
Phenols

phenols are aromatic compounds containing hydroxyl groups directly attached to the nucleus, and they are classified as monohydric, dihydric, trihydric phenols, etc, according as they contain one, two, three, etc hydroxyl group.

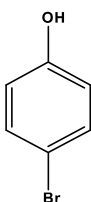


•Nomenclature:

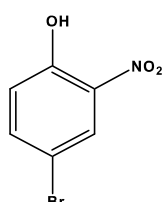
1. Numbering of the **ring begins at the hydroxyl-substituted carbon** and proceeds in the direction that gives the lower number to the next carbon atom bearing a substituent.



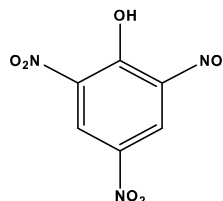
Phenol



p.bromo phenol

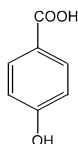


4-bromo-2-nitrophenol

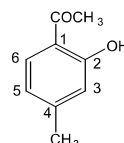


2,4,6 trinitrophenol

-Carboxyl and acyl groups take precedence over the phenolic hydroxyl in determining the base name. The hydroxyl is treated as a substituent in these cases.



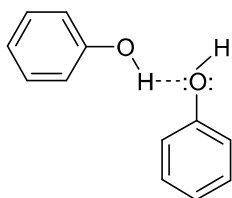
p-hydroxybenzoic acid



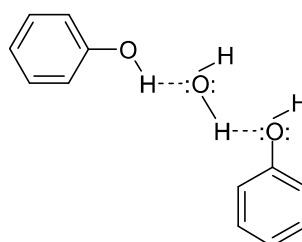
2-hydroxy-4-methylacetophenone

Physical properties:

The physical properties of phenols are **strongly influenced by the presence of the hydroxyl groups which permits phenols to form hydrogen bonds with other phenol molecules and with water** and are more soluble in water than arenes and aryl halides of comparable molecular weight:



A hydrogen bond between two phenol molecules

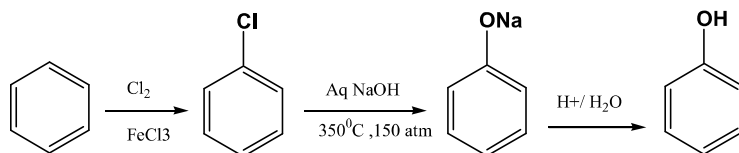


hydrogen bonds between water and phenol molecules

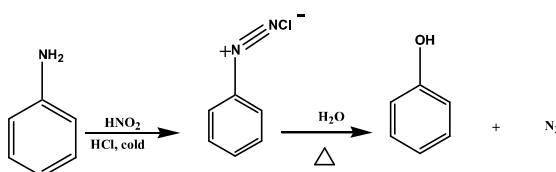
Preparation of Phenols:

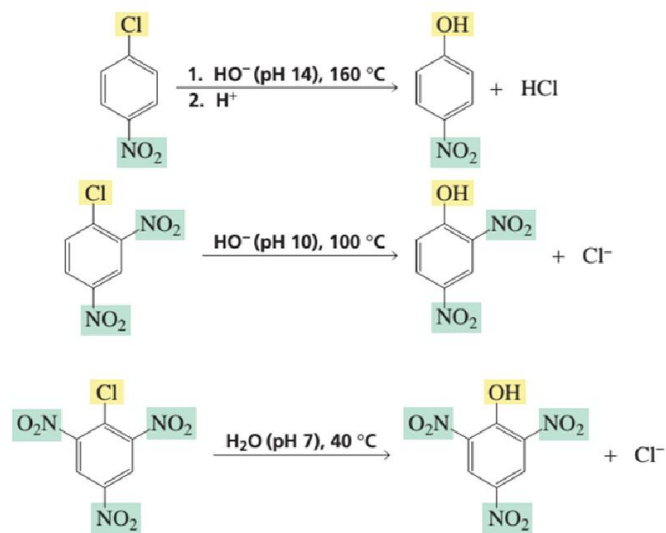
The preparation of phenols requires special methods because there is no direct way to introduce -OH group onto an aromatic ring. In laboratory we prepare phenol by

1) Dow process



2) Hydrolysis of diazonium

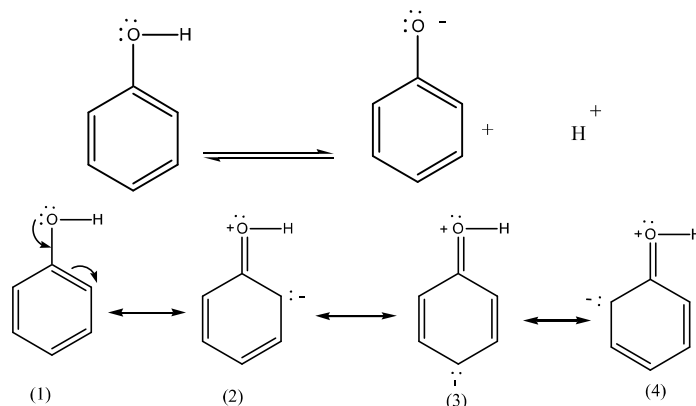




Acidity of phenols

Phenols are **more acidic than alcohols** but **less acidic than carboxylic acids**. Phenol for example will dissolve in **aqueous NaOH** whereas **cyclohexanol will not**.

Phenols however, unlike carboxylic acids, **do not dissolve in aqueous bicarbonate** solution because it is weaker acids than carbonic acid.

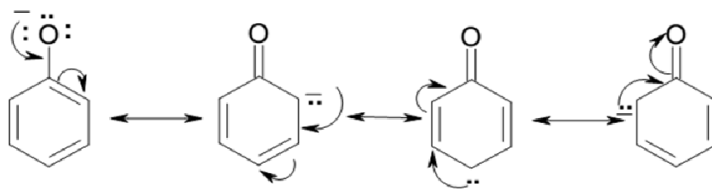


Resonance structure for phenol

The greater acidity of phenols (compared with alcohols) is due to:

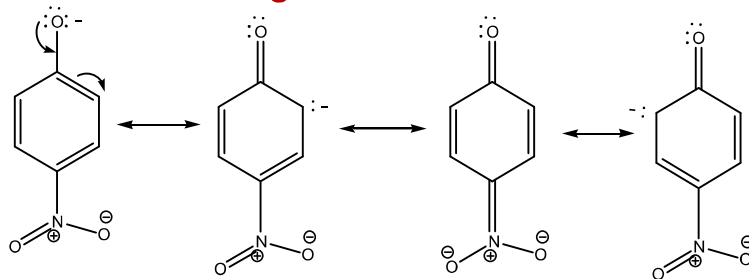
- The electron-withdrawing -I effect of the sp^2 carbon weakens the O-H bond of phenol compared with the effect of the sp^3 carbon of alcohols.

- Resonance **stabilization of the phenoxide ion relative to the alkoxide ion**:
The negative charge on the alkoxide ion $R-O^-$ (CH_3O^-) can **not be delocalized** but on phenoxide ion **phO⁻ the negative charge is delocalized** to the o- and p- ring positions.



- The electron attracting **substituents like -X or -NO₂ increase the acidity of phenols**, and electron **releasing** substituents like -NH₂ or CH₃ **decrease acidity**.

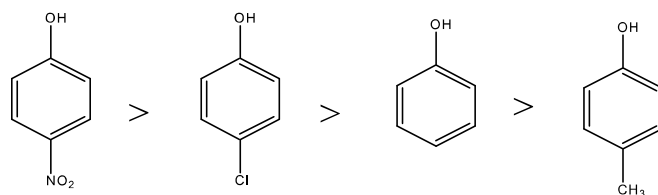
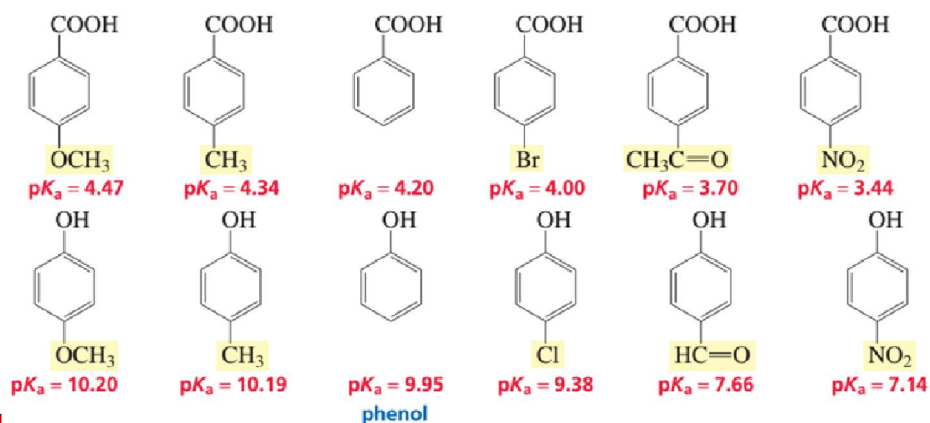
- An **ortho and para nitro group greatly stabilizes** the phenoxide ion by **electron-withdrawing resonance effect**.



electronegative oxygens of the nitro group **accommodate** all the negative charge.

The more deactivating (electron withdrawing) the substituent, the more it increases the acidity of a COOH, an OH, or an $^+NH_3$ group attached to a benzene ring.

electron withdrawal decreases reactivity toward electrophilic substitution and increases acidity, whereas electron donation increases reactivity toward electrophilic substitution and decreases acidity.



The relative strength of phenols as acids are as follows:

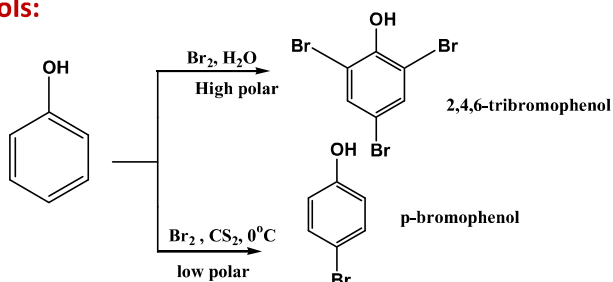
Reactions

phenols undergo **electrophilic aromatic substitution** reaction **much more** readily as compare **to benzene**. The -OH group in phenol is an **o-,p-director and activator**.

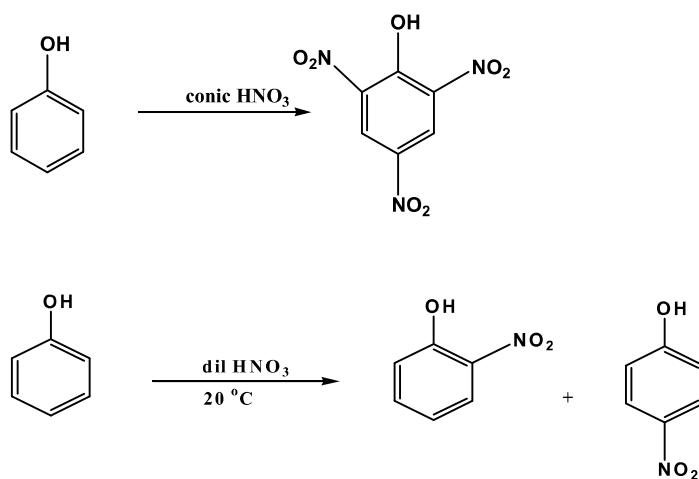
a) Electrophilic aromatic substitution(involving ring)

The most chemical property of a phenol is the high reactivity of its ring toward electrophilic substitution.

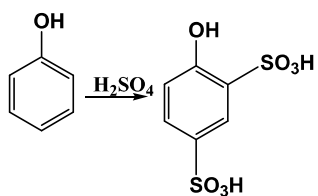
1. a-Halogenation of phenols:



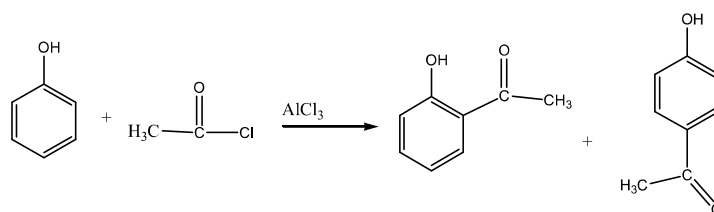
b- Nitration of phenols:



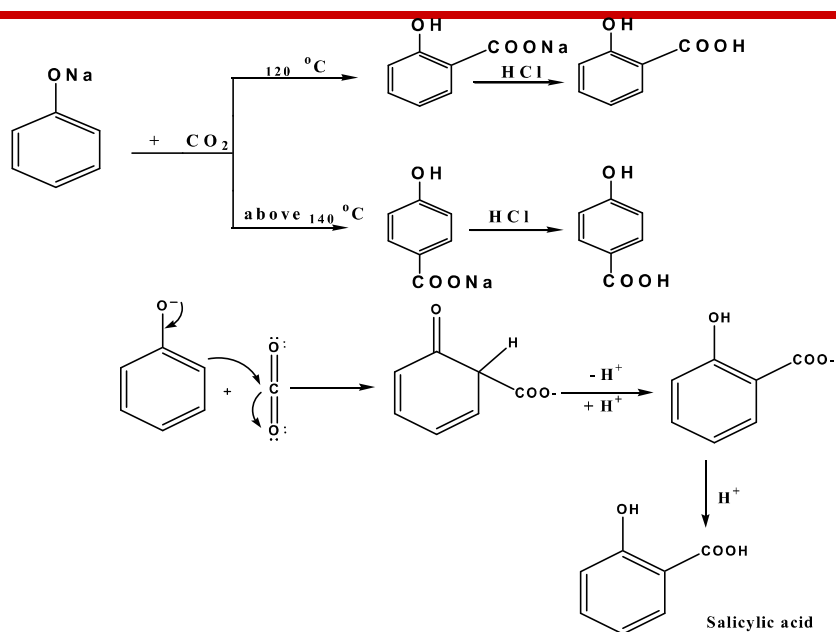
c. Sulphonation of phenol



d. Friedel -craft acylation



e. Carbonation of phenols (Kolbe reaction):



b) Reaction in which the O-H bond is broken.

Esterification

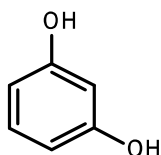
phenol + acetic anhydride $\longrightarrow$ phenyl acetate

Applications



Applications

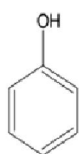
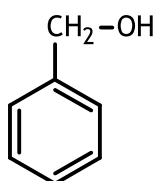
Resorcinol



used as Keratolytic in acne,, ringworms, eczema & psoriasis

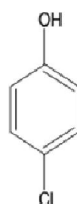
Benzyl alcohol is used as a preservative in vials of injectable drugs.

Also, it has a local anesthetic action



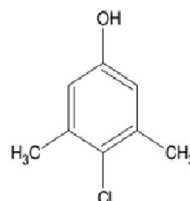
Phenol
(Carbolic acid)

(PC = 1)
cauteric agent
dogs and snake
bites



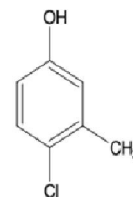
p-chlorophenol

(PC = 3.9)
lozenges



chloroxylenol

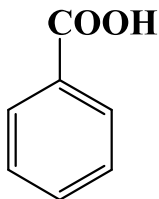
(Dettol, PC = 4.8)
Topical antiseptic



Chlorocresol

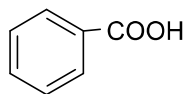
Phl. preservative

Aromatic Carboxylic acid



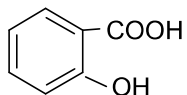
Aromatic Carboxylic acids

Aromatic carboxylic acids are compounds **containing one or more carboxyl groups**, which are directly attached to the nucleus. Those acids in which the carboxyl group occurs in the side chain may be regarded as **aryl substituted aliphatic acids**, but they are also classified as **aromatic acids**, since they exhibit aromatic properties due to **the presence of benzene ring**.



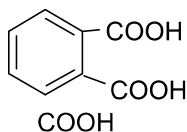
benzenecarboxylic acid

benzoic acid



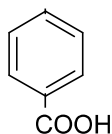
o-hydroxybenzenecarboxylic acid

salicylic acid



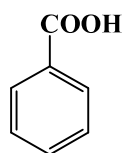
1,2-benzenedicarboxylic acid

phthalic acid

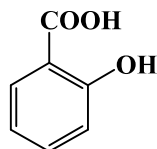


1,4-benzenedicarboxylic acid

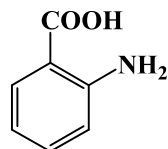
terephthalic acid



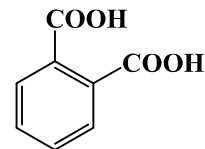
benzoic acid



salicylic acid



anthranilic acid



phthalic acid

Physical properties:

The melting points and boiling points of carboxylic acids are higher than those of alcohols of comparable molecular weight and indicate strong attractive forces between molecules. Carboxylic acids usually form a very unique and strong intermolecular hydrogen bonding between two molecules that some carboxylic acids exist as hydrogen-bonded dimer even in the gas phase.

Acidity of Carboxylic Acids

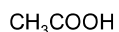
Any effect that results in electron withdrawal from the negatively charged center is a stabilizing effect because it spreads the charge. Thus, groups that withdraw electrons by inductive effect increases acidity while electron donating groups act in the opposite direction. Benzoic acid is a stronger acid than acetic acid.

Acidity of Carboxylic Acids :

Carboxylic Acids (pKa ~5) are more acidic than **alcohols (pKa 15-18)** and **phenols (pKa ~ 9-10)**. They dissolve in aqueous solutions of sodium hydroxide and sodium bicarbonate to form soluble sodium salts. The **high relative acidity of carboxylic acids** is attributed to factors which **stabilize the carboxylate anion**; namely the **inductive and the resonance effect of the carbonyl group**.

Benzoic acid is a stronger acid than acetic acid. why?

Carboxylic Acid:



pKa

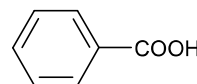
4.8

acetic acid



4.3

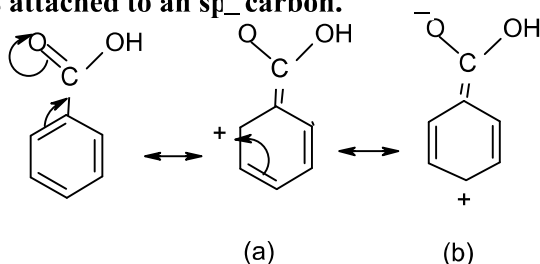
acrylic acid



4.2

benzoic acid

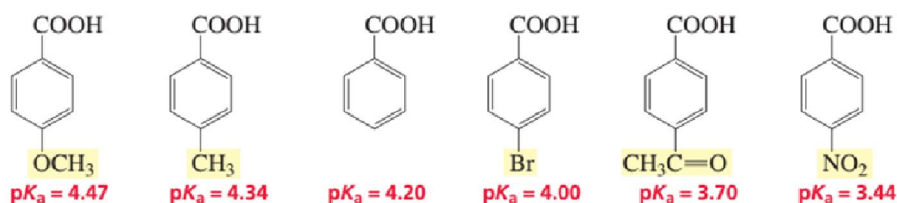
Aromatic acid is more acidic than aliphatic acid: as carboxyl group is attached to **sp² hybridized carbon** and **ionizes to a greater extent** than one that is attached to an sp³ carbon.



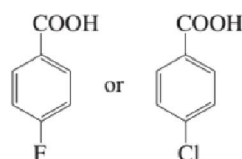
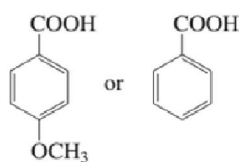
* Electron **withdrawing groups** substitution (Cl, Br, NO₂, CHO, CN), **↑ acidity**.

* **Electron donating groups** substitution (OH, NH₂, OCH₃, -R), **↓ acidity**.

electron withdrawal decreases reactivity toward electrophilic substitution and increases acidity, whereas electron donation increases reactivity toward electrophilic substitution and decreases acidity.



Which of the compounds in each of the following pairs is more acidic?



The most pronounced effects are observed when **strongly electron-withdrawing substituent at positions ortho** to the carboxyl group. **An ortho-nitro substituent, for example, increases the acidity** of benzoic acid **100- fold**.

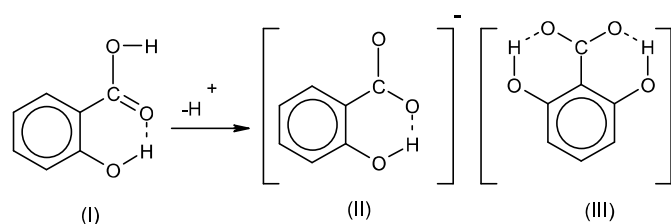
Substitutions effects **are small** at **position meta and para** to the carboxyl. Interestingly, **all ortho substituted benzoic acids** are **stronger acids** than the corresponding **para isomers**,

Intramolecular hydrogen bonding greatly influence the acid strength

The pK_a for *o*-hydroxybenzoic acid (salicylic acid) is 2.98, while the value for the *para* isomer is 4.58.

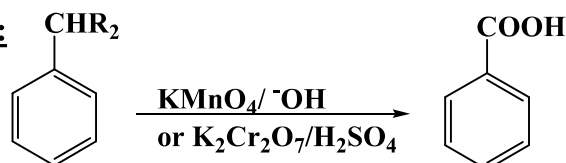
Internal hydrogen bonding between the **OH** and **COO⁻** group of the conjugate base of the **ortho** isomer **stabilizes** it and results in an **increased acidity** (See, structures I & II).

In **2,6 dihydroxybenzoic acid**, both phenolic **OH** groups participate in **hydrogen bonding** ; in the anion of this acid, the **negative charge** is spread over **two chelate rings** (III).

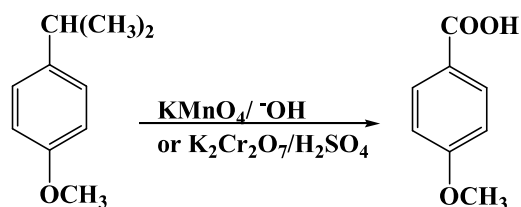


I-Preparation

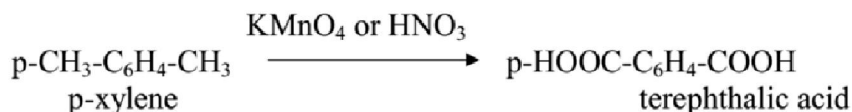
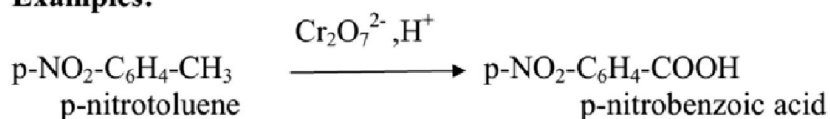
1) Oxidation of Alkylbenzenes:

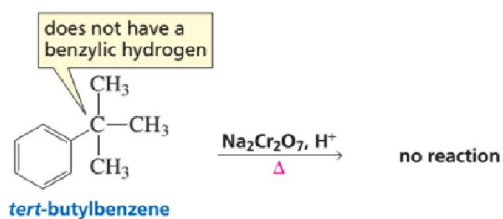
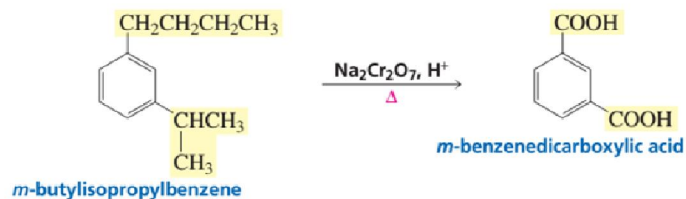
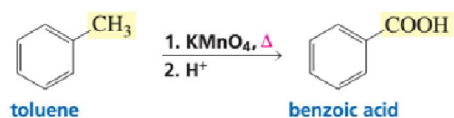


Examples:



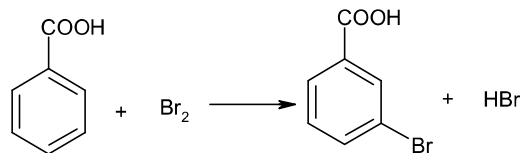
Examples:



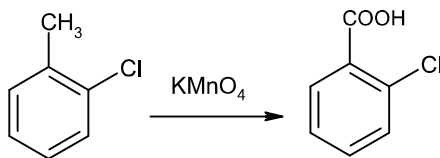


II-Reactions of carboxylic acids

1- Electrophilic Substitution: COOH is deactivating, m-directing group

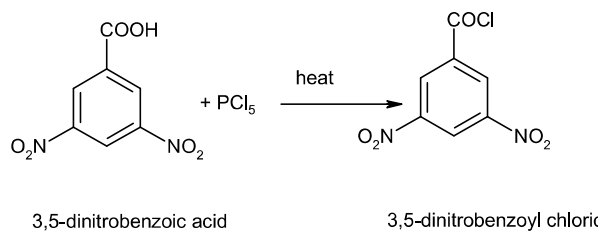


* Ortho and para-substituted benzoic acids may be obtained by oxidizing the corresponding toluene derivatives:

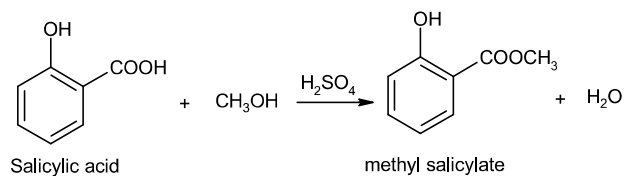


2-Reactions of the carboxyl group:

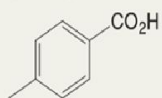
(i) **Preparation of Acyl Chlorides:** reacting acids with SOCl_2 , POCl_3 , PCl_5



ii) **Preparation of Esters:** Fischer esterification

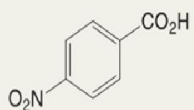


Which carboxylic acid would you expect to be stronger, A or B?



A

or

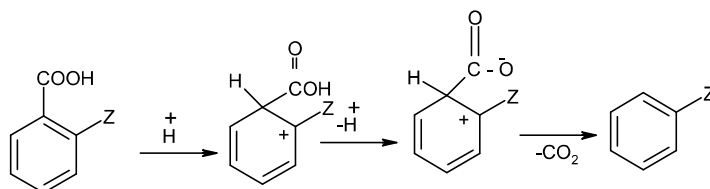


B

iii) Decarboxylation of Aromatic Acids:

1) **Heating with strong acid:** The reaction is accelerated by the presence of **electron-donating groups in the ortho and para position** and by the steric effect of groups in the ortho positions.

In benzene systems, the reaction is generally **limited to aromatic acids contain such groups**. In this method, **decarboxylation** takes place by **the aromatic S_E mechanism** with H⁺ as the electrophile and **CO₂ as the leaving group**



Z = an electron - donating group, e.g., NH₂ group

Esters

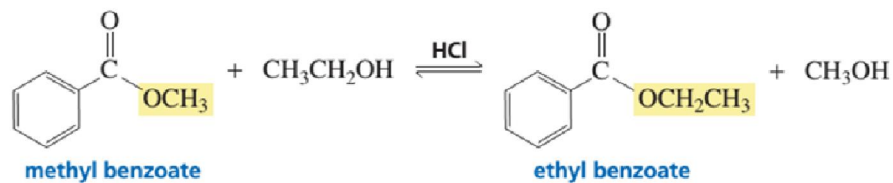
The names of esters are derived from the names of the alcohol (with the ending **-yl**) and the acid (with the ending **-ate** or **-oate**). The portion of the name derived from the alcohol comes first:



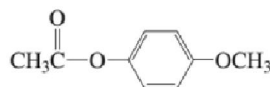
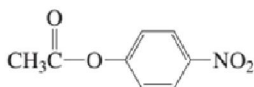
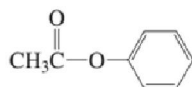
Reactions of Esters

An ester reacts with an alcohol to form a new ester and a new alcohol. This is an example of an **alcoholysis** reaction. This particular alcoholysis reaction is also called a **transesterification reaction** because one ester is converted to another ester.

a transesterification reaction

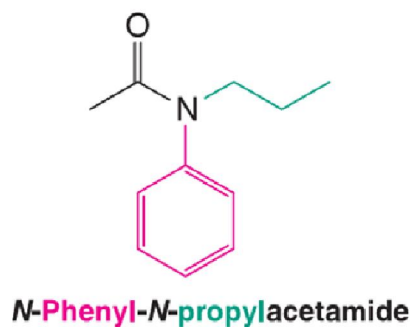


a. List the following esters in order of decreasing reactivity toward hydrolysis:



Amides

Amides that have no substituent on nitrogen are named by dropping **-ic acid** from the common name of the acid (or *-oic acid* from the substitutive name) and then adding **-amide**. Alkyl groups on the nitrogen atom of amides are named as substituents, and the named substituent is prefaced by *N*- or *N,N*-. Examples are



Organic Medicinal Chemistry

Ass Prof Mokhtar Al-Ghorafi

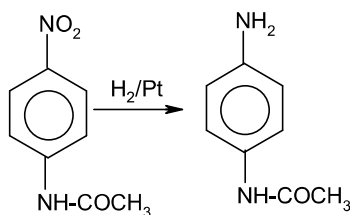
د. مختار الغرافي

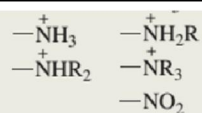
Aromatic amines

Aromatic amines are of two types, one in which the amino group is attached directly to the ring, and the other in which the amino group is in the side chain. The latter behave very much like the aliphatic amines and so may be regarded as aryl substituted aliphatic amines.

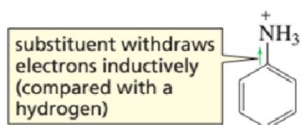
Preparation of Aromatic Amines:

1) From Nitro Compounds:



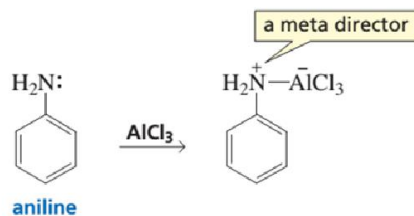


**Strongly
deactivating**



If a substituent is *more electron withdrawing than a hydrogen*, it will withdraw the σ electrons away from the benzene ring more strongly than will a hydrogen. Withdrawal of electrons through a σ bond is called **inductive electron withdrawal**. The $^+\text{NH}_3$ group is a substituent that withdraws electrons inductively because it is more electronegative than a hydrogen.

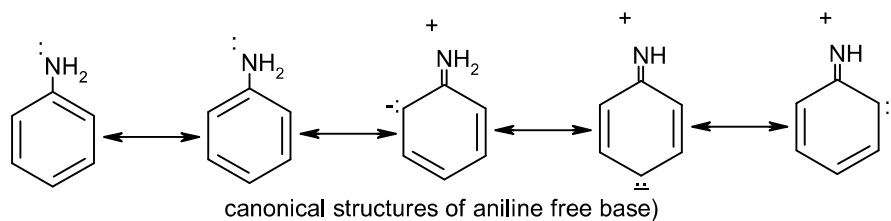
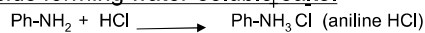
Aniline and *N*-substituted anilines also do not undergo Friedel–Crafts reactions. The lone pair on the amino group will complex with the Lewis acid (AlCl_3) that is needed to carry out the reaction, converting the NH_2 substituent into a deactivating meta director. As we have just seen, Friedel–Crafts reactions do not occur with benzene rings containing meta-directing substituents.



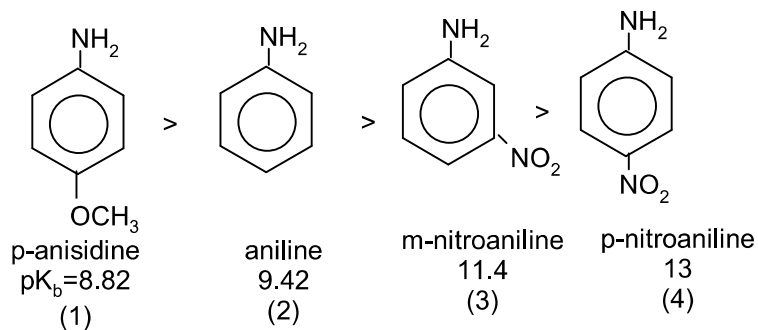
• Properties and Reactions of Aromatic Amines:

Basic Properties of Aromatic Amines:

Aromatic amines are basic. Water-insoluble aromatic amines dissolve in aqueous acids forming water-soluble salts.

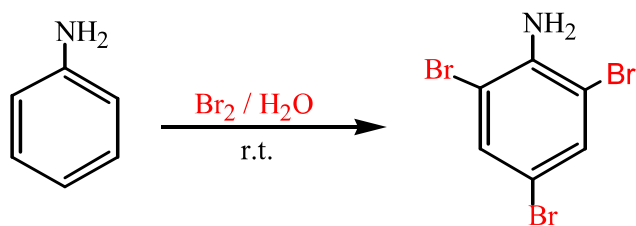


Electron releasing substituents increase basicity of aniline and electron withdrawing groups decrease it. e.g., the following aromatic amines are arranged in order of decreasing basic strength.

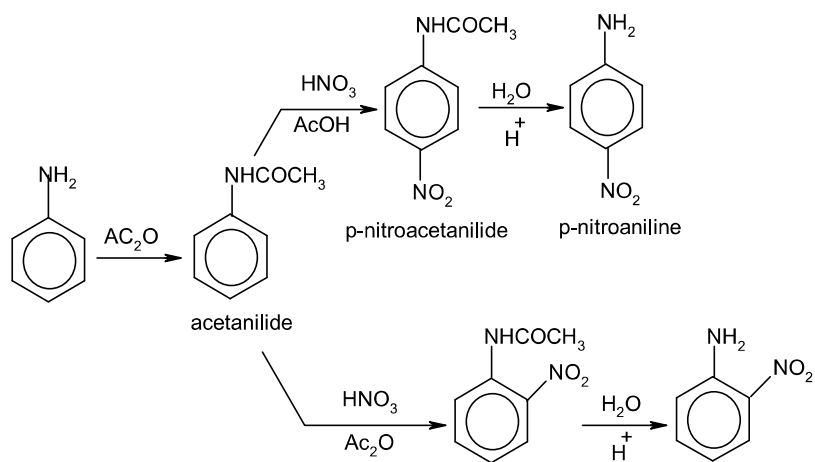


•Properties and Reactions of Aromatic Amines:
Basic Properties of Aromatic Amines:

•Ring substitution in aromatic amines (S_E reactions):

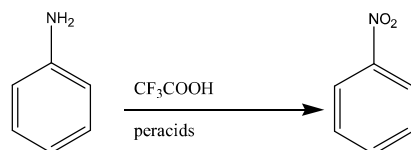


Nitration of Aromatic Amines

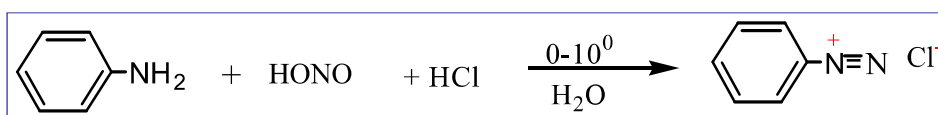


•Oxidation of aromatic amines

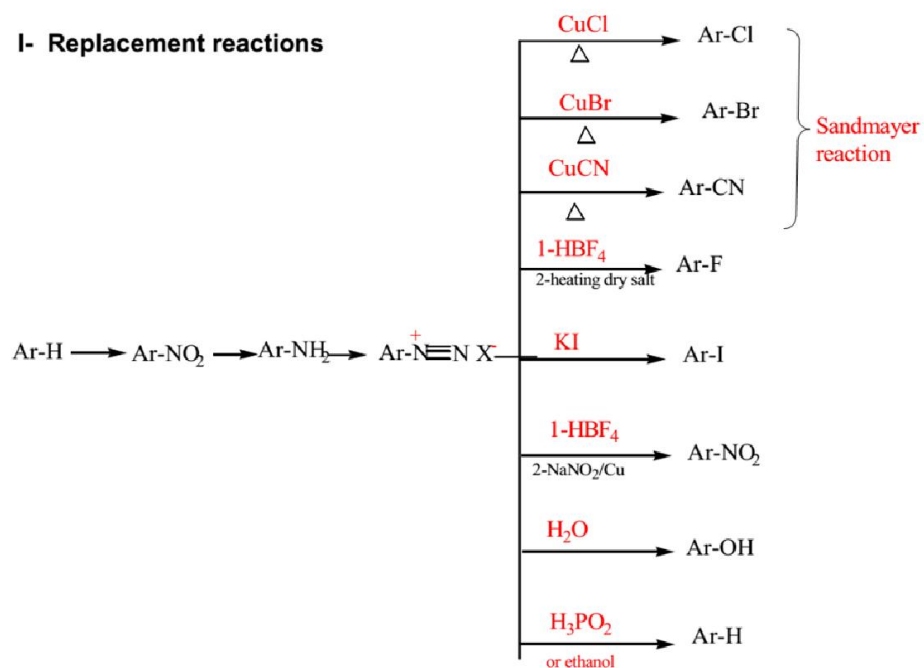
Aromatic amines are sensitive to oxidation.



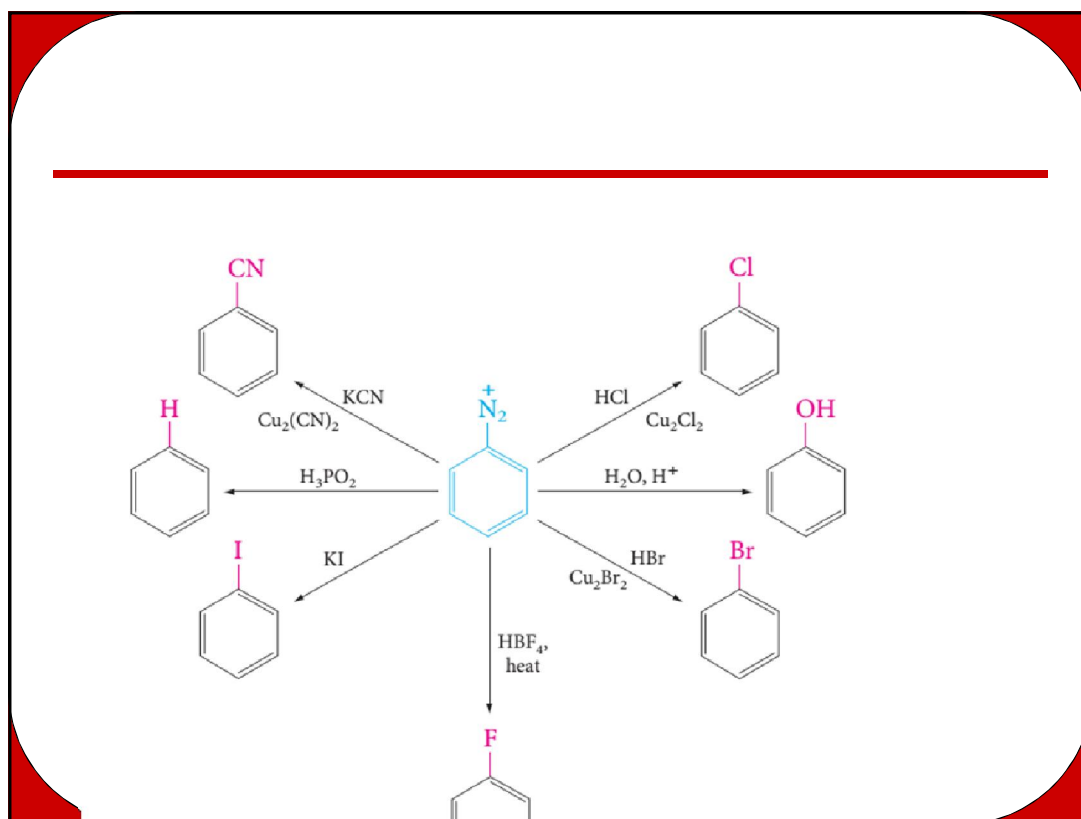
- Reaction with Nitrous acid: Primary arylamines



I- Replacement reactions



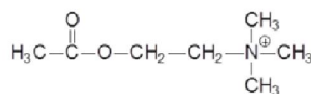
Reductive deamination reaction



How can *m*-dibromobenzene be prepared?

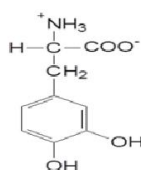
Design a route to 1,3,5-tribromobenzene from aniline.

The most important biological aliphatic quaternary ammonium compound is *acetylcholine*, the neurotransmitter of the parasympathetic and central nervous system, and the neuromuscular synapses. It is synthesized by the reaction of choline and acetyl CoA.

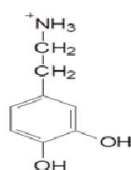


acetylcholine

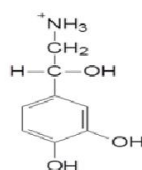
Cathecolamines and their analogues are major components in our body. 3',4'-dihydroxyphenylalanine (DOPA), formed from 4'-hydroxyphenylalanine (*tyrosine*), for example, is an intermediate in biosynthesis of *dopamine*. Dopamine takes part in signal transmission. *Noradrenaline*, synthesised from dopamine, is also a neurotransmitter. *Adrenaline*, formed from noradrenalin after methylation, has numerous biological functions



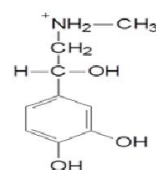
DOPA



dopamine



noradrenaline

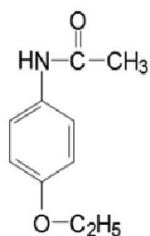


adrenaline

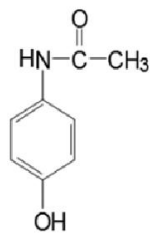
Drugs containing amino groups

Amines are very common derivatives among active pharmaceutical ingredients. Here only a few representatives with relatively simple structure are listed:

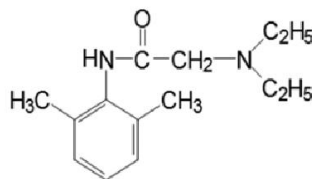
Phenacetin is not official in the Ph. Hg. VIII., only its active metabolite, called *paracetamol*. The derivatives of acetanilide are antipyretics and analgetics. *Lidocaine*, containing a diethylamino group is a medicine having both local anaesthetic and antiarrhythmic effect.



phenacetin



paracetamol



lidocaine

Azo dyes (those with the -N=N- linkage) account for 60–70% of dyes used in food and textile manufacture. Their acute toxicity is low but some azo dyes have been banned from foods because of the toxicity of dye breakdown products rather than the dye itself. The mechanisms by which tartrazine causes allergic reactions is not fully understood.



NITROSAMINES AND CANCER

A 1962 outbreak of food poisoning in sheep in Norway was traced to their ingestion of nitrite-treated fish meal. This incident immediately raised concerns about human consumption of nitrite-treated foods, because sodium nitrite is a commonly used food preservative. It can react with naturally occurring secondary amines present in food, to produce nitrosamines, which are known to be carcinogenic. Smoked fish, cured meats, and beer all contain nitrosamines. Nitrosamines are also found in cheese, which is not surprising because some cheeses are preserved with nitrite and cheese is rich in secondary amines. In the United States, consumer groups asked the Food and Drug Administration to ban the use of sodium nitrite as a preservative. This request was vigorously opposed by the meat-packing industry.

